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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,482	PETKOVICH ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 83-95,97-102 and 104-112 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 83-95,97-102,104-112 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The finality of the Office action mailed August 13, 2002 is hereby withdrawn in view of the new ground(s) of rejection.

Claims 83-95, 97-102 and 104-112 are pending.

During a telephone conversation conducted on February 12, 2003, Dr. John Hunt requested an extension of time for three MONTH(S) and authorized the Commissioner to charge Deposit Account No. 02-2553 the required fee of $ 920.00 for this extension.

Specification

The disclosure is objected to because of the paper and computer readable forms of the Sequence Listing are not identical. The paper copy contains 35 sequences while the computer readable form has 43 sequences.

A substitute paper copy of the Sequence Listing identical to the computer readable form in the file is required. It should be accompanied by the statement the two forms are identical and by the amendment directing the entry of a substitute Sequence Listing.

Claim Objections

Claims 83, 89 and 90 are objected because of the following.

In claims 83 and 90, the proper recitation of the Markush group requires "or" before the last member of the group (line 8).

Claim 89 is objected because of the following. The Markush group requires "or" before "SEQ ID NO:32" at two occurrences.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass all polypeptides of any function or that oxidize/hydroxylate retinoid and that bind to any antibody specific for SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:32. The Examiner is unable to locate adequate support in the specification for such polypeptides. Thus there is no indication that polypeptides encompassed by claims 97-102 and 104-112 were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 83, 85-90, 92-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "a conservatively substituted amino acid variant" of the amino acid sequences encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a DNA that hybridizes thereto or to a degenerate variant thereof under specific conditions. This amounts to any structure having the same function as a protein encoded by SEQ ID NOs: 3, 5 or 31. The structural limitations are insufficient because while a substitution is required to be conservative any amino acid residue in the sequence and any number thereof can be substituted resulting in a completely novel structure that is not described. This is equivalent to a claim with no structural limitations wherein an enzyme is defined by the function only. Furthermore, the function described only as "oxidizes/hydroxylates a retinoid" encompasses many different activities and substrate specificities. In addition, a genus of degenerate variants of SEQ ID NOs: 3, 5 or 31 is enormous.

Claims 83, 85-90, 92-95 and 107-112 are directed to polypeptides that oxidize or hydroxylate a retinoid or retinol or retinoic acid or all-*trans* retinoic acid at any position. Therefore, they encompass a genus of polypeptides described by broad function. The specification teaches only one species of the claimed genus, an all-*trans* retinoic acid hydroxylase that specifically hydroxylates all-*trans* retinoic acid at the C4-and the C18-position of the β-ionone ring and oxidizes all-*trans* retinoic acid at the C4-position of the β-ionone ring. The specification does not teach polypeptide species with any other retinoid oxidizing/hydroxylating activity, i.e, said activity with substrate specificity as broad as any retinoid, i.e., retinoic acid (RA), retinal, retinol in every stereo configuration as well as undescribed natural and artificial variants thereof (see the specification, paragraph bridging pages 5 and 6).

Furthermore, according to the definition of "retinoid", the genus of retinoids encompasses "a group of compounds which includes retinoic acid, vitamin A (retinol) and a series of natural and synthetic derivatives that an exert profound effects on development and differentiation in a wide variety of systems" (specification, paragraph bridging pages 4 and 5). The specification does not discloses any species within the genus of retinoids other than naturally occurring retinoic acid and derivatives thereof. There is no description of any synthetic derivative thereof or any natural or synthetic compound that can be construed as exerting profound effects on development and differentiation in a wide variety of systems. Therefore, the genus of retinoids

encompasses compounds of different structures and functions and the specification fails to disclose the correlation between structure and function common to all members of the genus.

In addition, claims 97-102 and 104-106 are drawn to a polypeptide that binds to an antibody specific for SEQ ID NOs: 2, 4 or 32 or is encoded by a DNA that hybridizes to the DNA encoding thereof and has no known function.

Therefore, the claims are drawn to a genus of polypeptides of undefined structures having any function.

The genus of polypeptides that comprises these above polypeptide molecules is a large variable genus encompassing many different proteins and fragments thereof. Many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims, including partial sequences. Said genus encompasses both polypeptides having an enzymatic activity and inactive variants thereof as well polypeptides with undisclosed function. The specification fails to provide identifying characteristics and/or correlation between structure and function common to all members of the genus.

Furthermore, claims 85 and 92 are drawn to polypeptides encoded by nucleotide sequences that are part of fish genome. This part of rejection comprises polypeptides with a narrow function such as a retinoic acid inducible polypeptides having all-*trans*

retinoic acid 4-hydroxylase. The specification teaches only a single species of the claimed diverse genus, an all-*trans* retinoic acid 4-hydroxylase from zebrafish. The recitation of "fish genome" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of proteins the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Thus, a polypeptide other than a polypeptide having 1) all-*trans* retinoic acid 4-hydroxylase activity and 2) an amino acid sequence of SEQ ID NO: 2, 4 or 32 or that is encoded by a DNA that hybridizes under highly stringent conditions to SEQ ID NO:3, 5

or 31 lacks sufficient written description needed to practice the invention of claims 83-95, 97-102 and 104-112.

Claims 83, 85-90, 92-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a all-*trans* retinoic acid 4-hydroxylase encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a sequence that hybridizes thereto under highly stringent conditions, does not reasonably provide enablement for a conservatively substituted amino acid variant thereof, a retinoid oxidase of any substrate specificity that is encoded by a sequence that hybridizes to SEQ ID NOs: 3, 5 or 31 or a degenerate variant thereof and a conservatively substituted amino acid variant thereof as well as a polypeptide that oxidizes/hydroxylates retinoid or having unknown function that binds to an antibody specific for SEQ ID NOs: 3, 5 or 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible derivatives having the desired enzymatic activities.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.

1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claim, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is

unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that is claimed in claims 83, 85-90, 92-95, 97-102 and 104-112 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the requisite activity. The specification does not teach the structure that is responsible for a specific all-*trans* retinoic acid 4-hydroxylase activity as compared to any other retinoid oxidizing activity;(B) the general tolerance of a protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. This reasoning is also applicable to cytochrome P450 structures comprising the heme binding region because there is no guidance provided as to what are residues that are responsible for the substrate specificity of the enzymes of the instant invention.

Furthermore, degenerate variants of SEQ ID NOs: 3, 5 or 31 encompass an enormous number of molecules. The specification does not provide any guidance as to

which of these degenerate variants can be used, so that a DNA that hybridizes thereto would encode a protein with the requisite properties.

With regard to claims 85 and 92, the rejection applies because the specification enables only for polypeptides that are encoded by DNAs that hybridize to SEQ ID NO: 3, 5 or 31 under highly stringent conditions, it does teach how to obtain variant polypeptides of unknown homology to SEQ ID NO:2, 4 or 32.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a number of amino acid modifications of SEQ ID NOs: 2, 4 or 32. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a protein having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claims 97-102 and 104-106 are drawn to proteins with no function. Applicants have not provided sufficient guidance as to what is the function of proteins encompassed by the claims.

The state of the art does not allow the predictability of the properties based on the structure. Therefore, one skilled in the art would require guidance as to how to use a polypeptide of unknown function that binds to an antibody specific for SEQ ID NOs: 2,

4 or 32 or is encoded by a DNA that hybridizes to a DNA encoding thereof in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83-90, 92-95 recite "conservatively substituted amino acid variant thereof". There are no clear assigned definitions of the term "conservatively substituted amino acid variant" in the art.

Claims 97-102 and 104-112 are confusing because they recite an antibody that is elicited by SEQ ID NO:2, 4 or 32 and by an epitope of unknown structure.

Claims 83-86, 89-92, 95 and 107-112 recite "retinoid". This term is defined as comprising "a series of natural and synthetic derivatives" (emphasis added). The metes and bonds of "derivative" are neither disclosed in the specification nor clearly known in the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Duell et al. (1992).

Duell et al. (form PTO-1449 filed February 6, 2003, reference 6, J. Clin. Investigation (1992), 90,1269-1274) teach a retinoic acid induced all-*trans* retinoic acid 4-hydroxylase activity in human skin microsomes. They teach that said activity catalyzes conversion of RA to 4-OH RA and 4-oxo RA (abstract, page 1271).

The microsomal fraction having the requisite activity contains a polypeptide with said activity. Said peptide is "isolated" from its natural environment. Therefore, the Duell et al. reference anticipates claims 83-95, 97-102 and 104-112.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Duell et al. (1994).

Duell et al. (form PTO-1449 filed February 6, 2003, reference 6, J. Investigative Dermatology (1994), Vol. 102, page 641, SID abstracts, abstract 704) teach a unique

cytochrome P450 that has retinoic acid induced all-*trans* retinoic acid 4-hydroxylase activity but does not metabolize 9-cis or 13-cis retinoic acid. They demonstrated said activity in human skin microsomes.

The microsomal fraction having the requisite activity contains a polypeptide with said activity. Said peptide is "isolated" from its natural environment. Therefore, the Duell et al. reference anticipates claims 83-95, 97-102 and 104-112.

Claims 97, 99, 101 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Vetter et al.

Vetter et al. teach the amino acid sequence of an inducible cytochrome P-450 protein from Periwinkle (*Catharanthus roseus* L.) (page 1002, Figure 3.). Since an epitope is not limited to a specific fragment, this polypeptide will bind to an antibody elicited by an epitope of some five, for example, amino acids within the conserved region of SEQ ID NOs: 2, 4 or 32 and, therefore anticipates claims 97, 99, 101 and 104-112.

Claims 97, 99, 101 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Shen et al.

Shen et al. teach the amino acid sequence of a mouse cytochrome P-450 protein (page 11485, Figure 3.). Since an epitope is not limited to a specific fragment,

this polypeptide will bind to an antibody elicited by an epitope of some five, for example, amino acids within the conserved region of SEQ ID NOs: 2, 4 or 32 and, therefore anticipates claims 97, 99, 101 and 104-112.

Response to Arguments

Applicant's arguments filed May 31, 2002 have been fully considered but they are not persuasive.

Applicants argue that claims 97-102 and 104-112 do not introduce the new matter because the specification on page 36 teaches that "antibodies can be used to detect the proteins of the invention, portions thereof or closely related isoforms in various biological materials" (page 10). This is not persuasive because there is support for an antibody and a method of use thereof but not for proteins that can be detected using said antibodies.

With regard to conservative variants, applicants disagree that they amount to any protein having the desired function (pages 11-12). Applicants assert that "it is only conservatively substituted variants of these proteins that are claimed. The claim includes only those variant proteins in which an individual amino acid is substituted for another amino acid of protein to have function. ... while it is admitted there is no limitation on the number of such substitutions that might be made, any such substitution is clearly based on one of basic claimed structures(a protein encoded by the sequence

that hybridizes to SEQ ID NO:3, 5, etc.) and would be known to the skilled person" (page 12, 2nd paragraph). This is not persuasive because claims are not drawn to proteins having substitutions from other proteins. Ad in any event, there is no limitation on the number and location of residues to be substituted.

Applicants further argue with regard to the function that "applicants reasonable expect that P450RAI oxidizes the 18 position of the β-ionone ring as well as the 4 position, and that P450RAI oxidizes retinol as well as RA (see page 3, lines 23-26)" (page 13, 2nd paragraph). The specification on page 3, lines 23-26 reads differently. However, on page 3, lines 27-30, it provides support for the 4 position of β-ionone ring of RA. However, the claims recite much broader specificity expanding the scope of the claims to encompass retinoid oxidizing enzymes of different function and properties. With regard to the 102 rejection, applicants argue that "the antibody is elicited by an epitope located within a specified unconserved region of the protein" (page 17). This is not persuasive because within this region the proteins of the instant invention share a few identical or conservatively substituted amino acids with the proteins of the references. An antibody elicited by such fragment would cross react with many proteins including the proteins of the instant invention and the references.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Frolik et al. (1979, form PTO-1449 filed February 6, 2003, reference 8) teach all-*trans* retinoic acid 4-hydroxylase activity in hamster trachea and liver.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

February 12, 2003